Ooplasm Transfer To Treat Infertility

Biological Response Modifiers Advisory Committee Meeting, May 9, 2002

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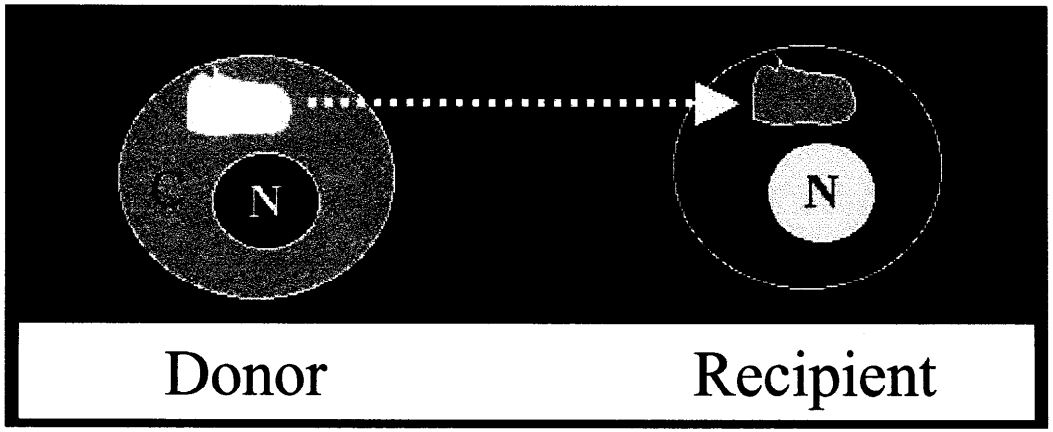
Biological Response Modifiers Advisory Committee, May 9-10, 2002

- Day 1: Ooplasm transfer in assisted reproduction
- Day 2: Potential inadvertent germline transmission during gene therapy

- **Transfer of genetic material into gametes — demonstrated effect of ooplasm transfer, potential, inadvertent risk of gene therapy**
- **Capable of producing heritable genetic modifications**

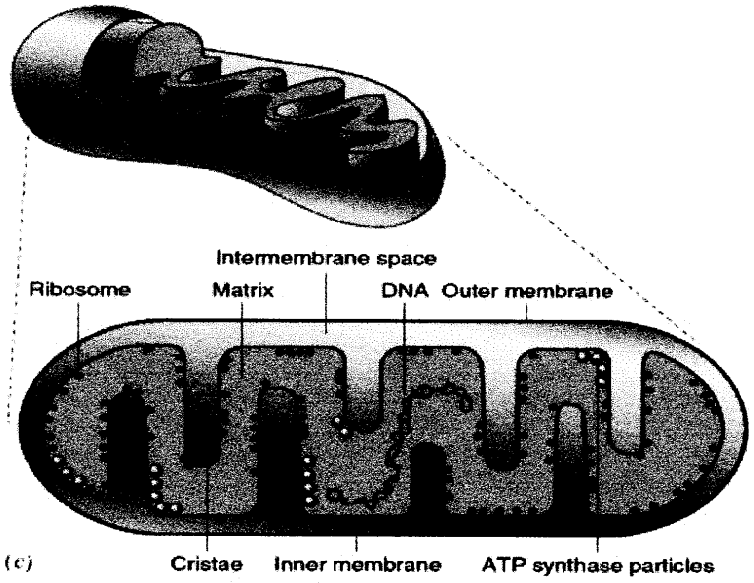
Ooplasm transfer to treat infertility



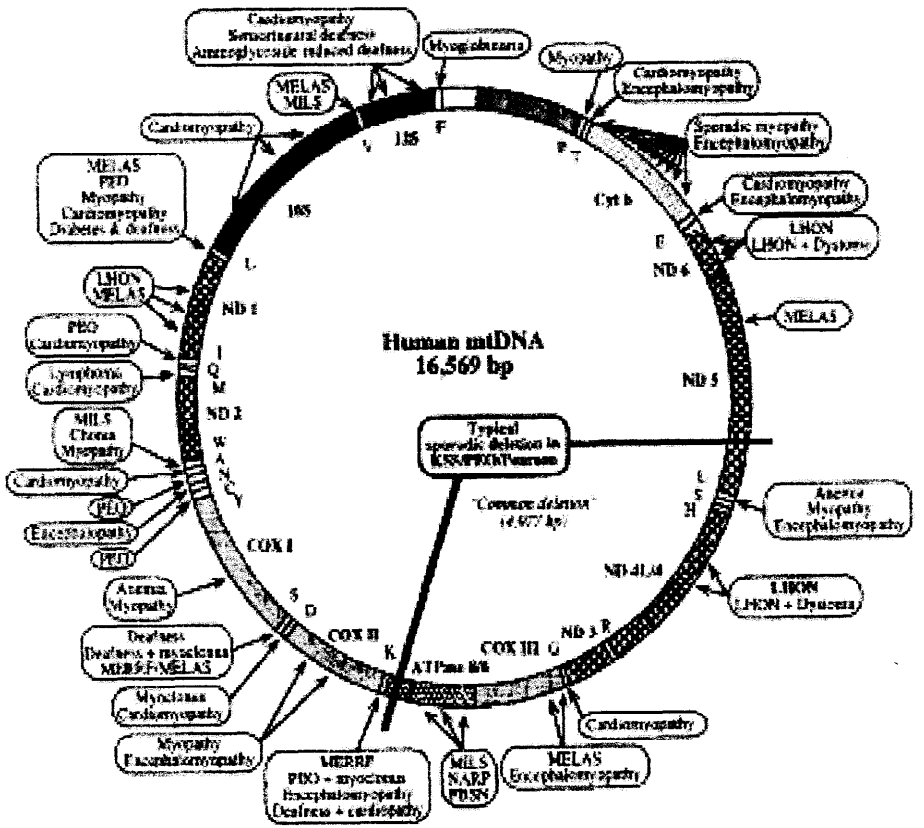
- **Cytoplasm (ooplasm) transferred from one unfertilized egg (oocyte) to another**
- **Ooplasm contains proteins, mRNAs, small molecules, and organelles**
  - **mitochondria**

Functions of mitochondria

- Aerobic respiration: production of energy (ATP) using oxygen.
- Fatty acid metabolism
- Intracellular ion balance
- Programmed cell death (apoptosis)



Mitochondria contain their own DNA



- **Very small genome (~17kb)**
- **37 distinct genes**
- **Unrelated individuals have distinct genotypes (used in forensics)**
- **Mutations are associated with human diseases**

From DiMauro, Seminars in Cell and Dev. Biology, 2002

Mitochondria are maternally inherited

- Sperm mitochondria do not persist
- Developing embryo (and resultant progeny) receive all mitochondria from the oocyte

Maternal mitochondrial DNA normally has a single genotype

- Homoplasmy : one genotype of mitochondria — common situation
- Heteroplasmy : more than one genotype of mitochondria — uncommon
- In heteroplasmy, mitochondrial genotypes can be partitioned unequally among tissues

What happens after ooplasm transfer?

- Barritt et al. (2001) *Human Reproduction*, Vol. 16., pp. 513-516, report that 2 children born after ooplasm transfer are known to have persistent heteroplasmy. The genotypes of both the ooplasm donor and the mother are represented in their tissues.

Ooplasm transfer: spread rapidly into clinical practice in the United States by 2001

- At least 23 children had been born using ooplasm transfer.
- Three U.S.clinics had published on this procedure.
- 5 additional clinics were advertising this procedure on the internet.

FDA Actions

- July, 2001: FDA sent letters to clinics and practitioners notifying them of our jurisdiction over ooplasm transfer. We advised them that an Investigational New Drug (IND) Application would be required to treat additional patients.

  http://www.fda.gov/cber/ltr/cytotrans070601.htm

- Late summer, 2001: Discussions with practitioners on the IND submission process

- Today: advisory meeting to discuss the laboratory and clinical science behind ooplasm transfer

FDA goals

- Are preclinical and clinical data supporting safety and efficacy of ooplasm transfer sufficient to justify risk of clinical trials?

- If additional data are needed, what types of data would be most informative?

FDA's Task:

- Weigh risks and benefits of ooplasm transfer

- Determine what safeguards need to be in place to ensure safety of human subjects